"Selectin" to Evade the Immune Response

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Merkel cell carcinoma (MCC) is an aggressive and lethal skin cancer caused by Merkel cell polyomavirus (MCPyV). The presence of CD8+ cytotoxic T cells in these tumors is correlated with survival, perhaps because MCPyV oncoproteins expressed in these tumors are targets for the immune response. However, only ~20% of patients with MCC have CD8+ T cells present in their tumors. In a recent study published in the Journal of Investigative Dermatology, Drs. Olga K. Afanasiev (University of Washington) and Paul Nghiem (University of Washington and Clinical Research Division) along with an international team of collaborators identify a possible mechanism for the low incidence of CD8+ T cells in these tumors. The authors demonstrate that E - selectin, a molecule involved in CD8+ T cell migration from blood vessels into skin, is downregulated in most MCCs, suggesting that current therapies modulating E - selectin expression may be useful in MCC treatment.

For a CD8+ T cell to enter the tumor, it must undergo a process called extravasation. Inflammation increases the expression of integrins, such as E - selectin, on cells lining the blood vessel lumen. Circulating CD8+ T cells recognize and bind these integrins (adhesion), then migrate out of the blood vessel following a chemokine gradient (transmigration). Once they are out of the blood vessel and in the tumor itself, CD8+ T cells recognize tumor - specific antigens and mediate a cytotoxic immune response.

Previous studies have demonstrated that squamous cell carcinoma evades the immune response by downregulating E - selectin expression (Clark, et al., 2008). To determine if MCC behaves in a similar manner Afanasiev et al., stained serial sections of MCC tumors with E - selectin specific antibodies, and found a 4 - fold reduction in E - selectin positive blood vessels within the tumor periphery compared to surrounding tissue ($p < 0.05$). Furthermore, patient survival was positively correlated with increased expression of E - selectin within the tumor. Consistent with E - selectin's importance in extravasation, the authors found very low or no CD8+ T cell infiltrate in 75% of the MCC they examined.

Local nitric oxide (NO) production has been shown to downregulate vascular E - selectin (Gehad et al., 2012). Afanasiev et al., stained for nitrotyrosine, a byproduct of local NO production, in MCC serial sections and found that 43% of tumors had moderate to high nitrotyrosine levels, while in only

6% of tumors nitrotyrosine was absent. In addition, nitrotyrosine levels were negatively correlated with E - selectin expression in intratumoral blood vessels ($p < 0.05$). Taken together, these data suggest that local production of NO may be one mechanism that MCC downregulates E - selectin and excludes CD8+ T cells from the tumor.

CD8+ T cells have the potential to control tumor progression, and this study identifies one mechanism by which MCC may regulate the tumor microenvironment to prevent CD8+ T cells from entering the tumor. Importantly, while increased E - selectin is associated with better prognosis for patients with MCC, in some other cancers E - selectin is a marker for increased metastatic potential, suggesting that drugs which modulate E - selectin levels in blood vessels may be useful only in certain tumors, such as MCC. "Therapeutic manipulation of the proposed mechanisms of T cell evasion will help establish the causation and clinical relevance of these findings in MCC patients. Furthermore, it may be appropriate to combine such treatment with adoptive virus - specific T - cell therapy to improve migration of T cells into tumors and thereby augment the efficacy of future immune therapy," according to Dr. Afanasiev.

Afanasiev OK, Nagase K, Simonson W, Vandeven N, Blom A, Koelle DM, Clark R, Nghiem P. 2013. Vascular e - selectin expression correlates with CD8 lymphocyte infiltration and improved outcome in merkel cell carcinoma. J Invest Dermatol. 133(8):2065 - 73.

See also: Clark RA, Huang SJ, Murphy GF, Mollet IG, Hijnen D, Muthukuru M, Schanbacher CF, Edwards V, Miller DM, Kim JE, Lambert J, Kupper TS. 2008. Human squamous cell carcinomas evade the immune response by down - regulation of vascular E - selectin and recruitment of regulatory T cells. J Exp Med. 205(10):2221 - 34.

See also: Gehad AE, Lichtman MK, Schmults CD, Teague JE, Calarese AW, Jiang Y, Watanabe R, Clark RA. 2012. Nitric oxide - producing myeloid - derived suppressor cells inhibit vascular E - selectin expression in human squamous cell carcinomas. J Invest Dermatol. 132(11):2642 - 51.

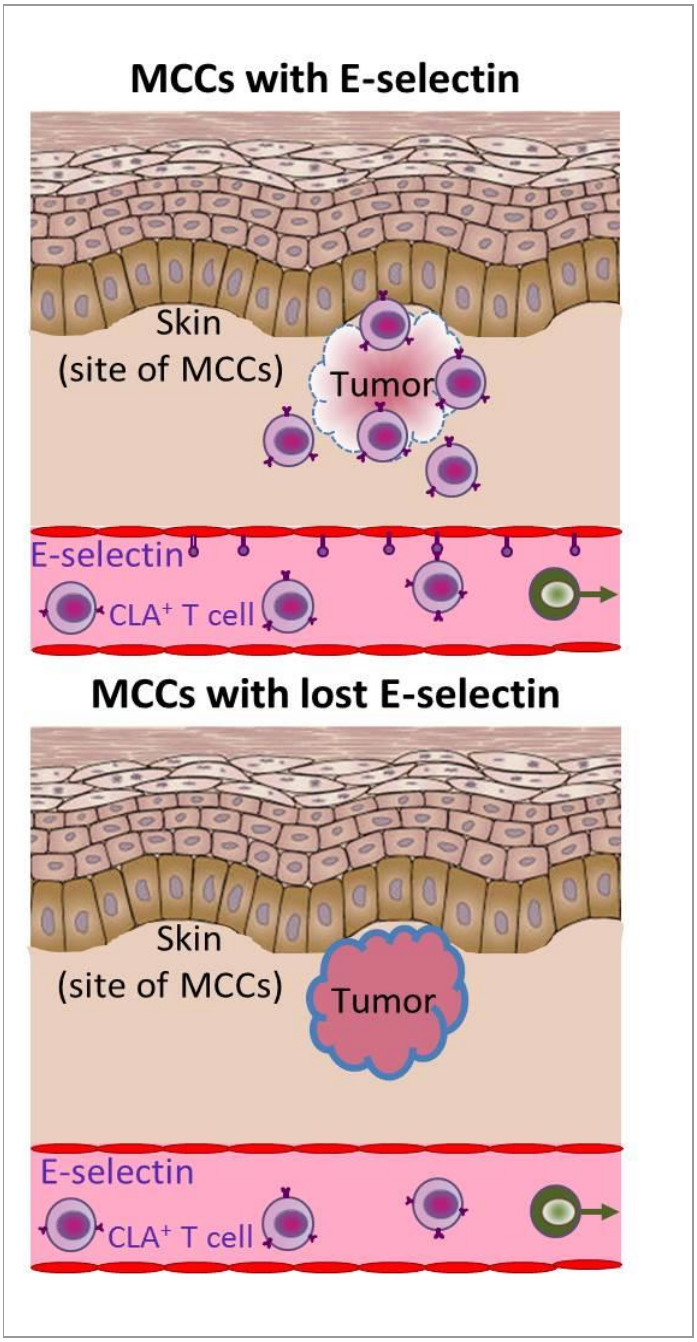

Image courtesy of Dr. Olga K. Afanasiev

Schematic of CD8+ T cell infiltration of Merkel cell carcinoma in the presence of E - selectin (top), or the exclusion of CD8+ T cells by downregulating E - selectin (bottom).